

What is claimed:

1. A method of decreasing intraocular pressure or improving ocular accommodation in an animal, including a human, comprising administering an intraocular pressure decreasing or accommodation improving amount of (A) a compound of formula (I):



wherein:

- a. Ar is a five or six membered heteroaryl ring having a first ring nitrogen and optionally second or third ring nitrogens, with the remaining ring atoms being carbon, oxygen, or sulfur, provided the first nitrogen of Ar is a quaternary nitrogen and Ar is not thiazolium, oxazolium or imidazolium;
- b. Y is substituted on the first ring nitrogen, with the proviso that if Ar is pyrazole, indazole, (1,2,3)-triazole, benzotriazole, or (1,2,4)-triazole, the second ring nitrogen is substituted with
 1. alkyl or alkoxycarbonylalkylene;
 - 15 2. Ar* {wherein, consistent with the rules of aromaticity, Ar* is C₆ or C₁₀ aryl or a 5- or 6-membered heteroaryl ring, wherein 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring may be fused to a benzene, pyridine, pyrimidine, pyridazine, pyrazine, or (1,2,3)triazine (wherein the ring fusion is at a carbon-carbon double bond of Ar*)}; or
 - 20 3. Ar*alkyl-, Ar*C(O)alkyl-, Ar*sulfonylalkyl-, or Ar*sulfinylalkyl-; and
- c. Ar can be substituted on ring carbon atoms
 1. with one or more substituents independently selected from the group
 - 25 consisting ω-alkylenesulfonic acid, carbamoyl, Ar*, Ar*-alkyl-, Ar*-O-, Ar*SO₂-, Ar*SO-, Ar*S-, Ar*SO₂NH-, Ar*NH, (N-Ar*)(N-alkyl)N-, Ar*C(O)-, Ar*C(O)NH-, Ar*NH-C(O)-, and (N-Ar*)(N-alkyl)N-C(O)-; or
 2. two adjacent substitutions together with their ring carbons form a C₆- or C₁₀- aromatic fused ring system; or
 - 30 3. two adjacent substitutions together with their ring carbons form a C₅-C₇ fused cycloalkyl ring having up to two double bonds including the fused double

bond of the Ar group, which cycloalkyl ring can be substituted by one or more of the group consisting of alkyl, alkoxycarbonyl, amino, aminocarbonyl, carboxy, fluoro, or oxo; or

4. two adjacent substitutions together with their ring carbons form a fused five to eight membered heterocycle, wherein the ring fusion is at a carbon-carbon double bond of Ar, wherein the heterocycle consists of ring atoms selected from the group consisting of carbon, nitrogen, oxygen, and $S(O)_n$, wherein $n=0, 1$, or 2 ; or
5. two adjacent substitutions together with their ring carbons form a fused five or six membered heteroaryl ring, wherein the ring fusion is at a carbon-carbon double bond of Ar, wherein the fused heteroaryl ring consists of ring atoms selected from the group consisting of carbon, nitrogen, oxygen, and sulfur;

d. Y is:

1. a group of the formula $-CH(R^5)-R^6$

(a) R^5 is hydrogen, alkyl-, cycloalkyl-, alkenyl-, alkynyl-, hydroxyalkyl, aminoalkyl-, dialkylaminoalkyl-, (N-[C_6 or C_{10}]aryl)(N-alkyl)aminoalkyl-, piperidin-1-ylalkyl-, pyrrolidin-1-ylalkyl, azetidinyllalkyl, 4-alkylpiperazin-1-ylalkyl, 4-alkylpiperidin-1-ylalkyl, 4-[C_6 or C_{10}]aryl piperazin-1-ylalkyl, 4-[C_6 or C_{10}]aryl piperidin-1-ylalkyl, azetidin-1-ylalkyl, morpholin-4-ylalkyl, thiomorpholin-4-ylalkyl, piperazin-1-ylalkyl, piperidin-1-ylalkyl, [C_6 or C_{10}]aryl, or independently the same as R^6 ;

(b) wherein R^6 is

(1) hydrogen, alkyl (which may be substituted by alkoxycarbonyl)-, alkenyl, alkynyl, cyano-, cyanoalkyl-, or R_s , wherein R_s is a [C_6 or C_{10}]aryl or a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur; or

(2) a group of the formula $-W-R^7$, wherein R^7 is alkyl, alkoxy, hydroxy, or R_s , wherein W is $-C(=O)-$ or $-S(O)_2-$;

(3) a group of the formula $-W-OR^8$ wherein R^8 is hydrogen or alkyl,

(4) a group of the formula $-CH(OH)R_s$; or

(5) a group of the formula $-W-N(R^9)R^{10}$, wherein

(a) R^9 is hydrogen and R^{10} is an alkyl or cycloalkyl, optionally substituted by

(i) $[C_6 \text{ or } C_{10}]$ aryl, or

(ii) a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains at least one and up to three atoms of N and, the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, said heteroaryl ring can be optionally substituted with one or more 1-pyrrolidinyl, 4- $[C_6 \text{ or } C_{10}]$ aryl piperazin-1-yl, 4- $[C_6 \text{ or } C_{10}]$ aryl piperidin-1-yl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, halo or (C_1-C_3) alkylenedioxy groups, or fused to a phenyl or pyridine ring, wherein the ring fusion is at a carbon-carbon double bond of the heteroaryl ring), or

(iii) a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur; or

(b) R^9 is hydrogen or alkyl and R^{10} is Ar^* ; or

(c) R^9 is hydrogen or alkyl, R^{10} is a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms are selected from the group consisting of oxygen, nitrogen and sulfur; or

(d) R^9 and R^{10} are both alkyl groups; or

(e) R^9 and R^{10} together with N form a heterocycle containing 4-10 ring atoms which can incorporate up to one additional heteroatom selected from the group of N, O or S in the ring, wherein the heterocycle is optionally substituted with $(C_6\text{-or } C_{10})$ aryl, $(C_6\text{-or } C_{10})$ arylalkyl, or a 5- or 6-membered heteroaryl ring containing at least one and up to three atoms of N for the 6-membered heteroaryl rings and from one to three atoms of N or one atom of O or S and zero to two atoms of N for the 5-membered heteroaryl rings, each such heteroaryl can

be optionally substituted with one or more 1-pyrrolidinyl, 4-[C₆ or C₁₀]arylpiperazin-1-yl, 4-[C₆ or C₁₀]arylpiperidin-1-yl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, halo or (C₁-C₃)alkylenedioxy; or

5 (f) R⁹ and R¹⁰ are both hydrogen; or

2. -NH₂, and

e. X is a pharmaceutically acceptable anion, which may be absent if the compound provides a neutralizing salt,

(B) a pharmaceutically acceptable salt of the compound,

10 wherein aryl, Ar or Ar* can be substituted with, in addition to any substitutions specifically noted, one or more substituents selected from the group consisting of acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxy carbonyl, alkoxy carbonylalkyl, alkyl, alkylamino, (C₁-C₃)alkylenedioxy, alkylsulfonyl, alkylsulfinyl, ω-alkylenesulfonic acid, alkylthio, allyl, amino, Ar*C(O)-, Ar*C(O)NH-, Ar*O-, Ar*-, Ar*-alkyl-, carboxy, carboxyalkyl, 15 cycloalkyl, dialkylamino, halo, trifluoromethyl, hydroxy, (C₂-C₆)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid (SO₃H), 1-pyrrolidinyl-, 4-[C₆ or C₁₀]arylpiperazin-1-yl-, 4-[C₆ or C₁₀]arylpiperidin-1-yl, azetidin-1-yl, and morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl; and

20 wherein heterocycles, except those of Ar or Ar*, can be substituted with, in addition to any substitutions specifically noted, acylamino, alkanoyl, alkoxy, alkoxy carbonyl, alkoxy carbonylalkyl, alkyl, alkylamino, alkylsulfonyl, alkylsulfinyl, alkylthio, amino, Ar*C(O)-, Ar*O-, Ar*-, carboxy, dialkylamino, fluoro, fluoroalkyl, difluoroalkyl, hydroxy, mercapto, sulfamoyl, or 25 trifluoromethyl.

2. The method of claim 1, comprising administering an intraocular pressure decreasing or accommodation improving amount of a compound of formula I, wherein Y is according to formula -CH(R⁵)R⁶.

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3. The method of claim 2, comprising administering an intraocular pressure decreasing or accommodation improving amount of a compound of formula I, wherein Y is according to formula -CH(R⁵)-W-R⁷.

4. The method of claim 2, comprising administering an intraocular pressure decreasing or accommodation improving amount of a compound of formula I, wherein Y is according to formula $-\text{CH}(\text{R}^5)-\text{W}-\text{Rs}$.

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5. The method of claim 1, comprising administering an intraocular pressure decreasing or accommodation improving amount of a compound of formula I, wherein:

c. Ar can substituted on ring carbon atoms

1. with one or more substituents independently selected from the group

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consisting hydrogen, acylamino, alkanoyl, alkanoylalkyl, alkoxy, alkoxy carbonyl, alkoxy carbonylalkyl, alkyl, ω -alkylenesulfonic acid, carbamoyl, carboxy, carboxyalkyl, cycloalkyl, halo, hydroxy, (C_2-C_6) hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid $(-\text{SO}_3\text{H})$, alkylsulfonyl (alkylSO_2-) , alkylsulfinyl $(\text{alkylSO}-)$, alkylthio, trifluoromethyl, Ar^* , $\text{Ar}^*-\text{alkyl}-$, $\text{Ar}^*-\text{O}-$, Ar^*SO_2- , $\text{Ar}^*\text{SO}-$, $\text{Ar}^*\text{S}-$, $\text{Ar}^*\text{SO}_2\text{NH}-$, Ar^*NH , $(\text{N}-\text{Ar}^*)(\text{N}-\text{alkyl})\text{N}-$, $\text{Ar}^*\text{C}(\text{O})-$, $\text{Ar}^*\text{C}(\text{O})\text{NH}-$, $\text{Ar}^*\text{NH}-\text{C}(\text{O})-$, and $(\text{N}-\text{Ar}^*)(\text{N}-\text{alkyl})\text{N}-\text{C}(\text{O})-$, wherein Ar^* may be substituted by one or more substituents as set forth above; or

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2. two adjacent substitutions together with their ring carbons form a C_6 - or C_{10} -aromatic fused ring system; or

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3. two adjacent substitutions together with their ring carbons form a C_5 - C_7 fused cycloalkyl ring having no double bonds except the fused double bond of the Ar group, which cycloalkyl ring can be substituted by one or more of the group consisting of alkyl, amino, aminocarbonyl, carboxy, fluoro, or oxo, wherein multiple substituents are located on different carbon atoms of the cycloalkyl ring, except in the case of alkyl, and fluoro substituents, which can be located on the same or different carbon atoms;

25

d. Y is:

1. a group of the formula $-\text{CH}(\text{R}^5)-\text{R}^6$

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(a) R^5 is hydrogen or alkyl;

(b) wherein R^6 is

(1) hydrogen, alkyl, alkenyl, alkynyl, cyano, cyanoalkyl, or Rs ,

wherein Rs is a $[\text{C}_6$ or $\text{C}_{10}]$ aryl or a heterocycle containing 4-10

ring atoms of which 1-3 are heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur; or

(2) a group of the formula $-W-R^7$, wherein R^7 is alkyl, alkoxy, hydroxy, or Rs, wherein W is $-C(=O)-$ or $-S(O)_2-$;

5 (3) a group of the formula $-W-OR^8$ wherein R^8 is hydrogen or alkyl,

(4) a group of the formula $-CH(OH)Rs$; or

(5) a group of the formula $-W-N(R^9)R^{10}$, wherein

(a) R^9 is hydrogen and R^{10} is an alkyl or cycloalkyl, optionally substituted by

10 (i) $[C_6 \text{ or } C_{10}]$ aryl, or

(ii) a 5- or 6-membered heteroaryl ring containing at least one and up to three atoms of N for the 6-membered heteroaryl ring and from one to three atoms of N or one atom of O or S and zero to two atoms of N for the 5-membered heteroaryl ring; said heteroaryl ring can be optionally substituted with one or more halo or $(C_1-$
15 $C_3)$ alkylenedioxy groups, or fused to a phenyl ring, or

(b) R^9 is hydrogen or alkyl and R^{10} is Ar^* ; or

(e) R^9 and R^{10} together with N form a heterocycle containing 4-10

20 ring atoms which can incorporate up to one additional heteroatom selected from the group of N, O or S in the ring, wherein the heterocycle is optionally substituted with $(C_6\text{-or } C_{10})$ aryl, $(C_6\text{-or } C_{10})$ arylalkyl, or a 5- or 6-membered heteroaryl ring containing at least one and up to three atoms of
25 N for the 6-membered heteroaryl rings and from one to three atoms of N or one atom of O or S and zero to two atoms of N for the 5-membered heteroaryl rings, each such heteroaryl can be optionally substituted with one or more halo or $(C_1-$
 $C_3)$ alkylenedioxy; or

30 (f) R^9 and R^{10} are both hydrogen;

or

2. $-NH_2$, and

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e. X is a pharmaceutically acceptable anion, which may be absent if the compound provides a neutralizing salt,

(B) a pharmaceutically acceptable salt of the compound,

wherein aryl, Ar or Ar* can be substituted with, in addition to any substitutions

5 specifically noted, with one or more substituents selected from the group consisting of acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, (C₁-C₃)alkylenedioxy, alkylsulfonyl, alkylsulfinyl, ω-alkylenesulfonic acid, alkylthio, allyl, Ar*C(O)-, Ar*C(O)NH-, Ar*O-, Ar*-, Ar*-alkyl-, carboxy, carboxyalkyl, cycloalkyl, halo, 10 trifluoromethyl, hydroxy, (C₂-C₆)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid (SO₃H); and

wherein heterocycles, except those of Ar or Ar*, can be substituted with, in addition to any substitutions specifically noted, acylamino, alkanoyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylsulfonyl, alkylsulfinyl, 15 alkylthio, Ar*C(O)-, Ar*O-, Ar*-, carboxy, fluoro, fluoroalkyl, difluoroalkyl, hydroxy, mercapto, sulfamoyl, or trifluoromethyl, wherein multiple substituents are located on different atoms of the heterocyclic ring, with the proviso that alkyl, alkylcarbonyl, and fluoro substituents can be substituted on the same carbon atom of the heterocyclic ring.

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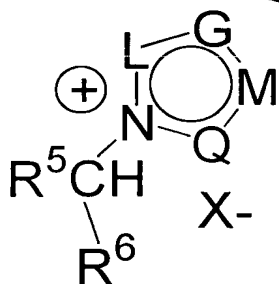
6. The method of claim 5, comprising administering an intraocular pressure decreasing or accommodation improving amount of a compound of formula I, wherein Y is according to formula -CH(R⁵)R⁶.

25 7. The method of claim 6, comprising administering an intraocular pressure decreasing or accommodation improving amount of a compound of formula I, wherein Y is according to formula -CH(R⁵)-W-R⁷.

8. The method of claim 6, comprising administering an intraocular pressure 30 decreasing or accommodation improving amount of a compound of formula I, wherein Y is according to formula -CH(R⁵)-W-Rs.

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9. The method of claim 1, wherein $Y-Ar^{\oplus} \bullet X^{-}$ is



(II)

wherein G, L, M, and Q are independently O, S, N, N-R^a, C, C-R^b, C-R^c, C-R^d,
wherein no more than one of G, L, M, or Q is O or S;

5 wherein

1. R⁵ is H;

2. R⁶ is

(1) cyano or

(2) a group of the formula -W-R⁷, wherein R⁷ is alkyl or Rs, and W is -
10 C(=O)- or -S(=O)-;

(3) a group of the formula -W-N(R⁹)R¹⁰, wherein

(a) R⁹ is hydrogen and R¹⁰ is an alkyl or cycloalkyl, optionally
substituted by

(i) [C₆ or C₁₀]aryl, or

(ii) a 5- or 6-membered heteroaryl ring, wherein the 6-membered

heteroaryl ring contains at least one and up to three atoms of N
and, the 5-membered heteroaryl ring contains from one to
three atoms of N or one atom of O or S and zero to two atoms
of N, said heteroaryl ring can be optionally substituted with
one or more 1-pyrrolidinyl, 4-[C₆ or C₁₀]arylpiperazin-1-yl, 4-
[C₆ or C₁₀]arylpiperidin-1-yl, azetidin-1-yl, and morpholin-4-
yl, piperidin-1-yl, halo or (C₁-C₃)alkylenedioxy groups, or
fused to a phenyl or pyridine ring, wherein the ring fusion is at
a carbon-carbon double bond of the heteroaryl ring);

25 3. R^a is alkyl, Ar*, Ar*alkyl, alkoxy carbonylalkylene-, Ar*C(O)alkyl-,
Ar*sulfonylalkyl-, or Ar*sulfinylalkyl-; and

4. R^b, R^c, and R^d are

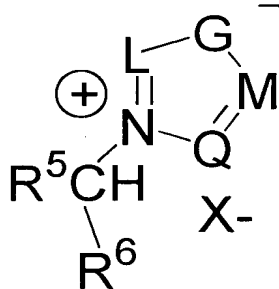
- 5 (a) independently selected from the group consisting hydrogen, acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, (C1-C3)alkylenedioxy, alkylsulfonyl, alkylsulfinyl, ω -alkylenesulfonic acid, alkylthio, allyl, amino, Ar^{*}C(O)-, Ar^{*}O-, Ar^{*}-, Ar^{*}-alkyl-, carboxy, carboxyalkyl, cycloalkyl, dialkylamino, halo, trifluoromethyl, hydroxy, (C2-C6)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid (SO₃H), 1-pyrrolidinyl-, 4-[C₆ or C₁₀]aryl piperazin-1-yl-, 4-[C₆ or C₁₀]aryl piperidin-1-yl, azetidin-1-yl, and morpholin-4-yl, piperidin-1-yl;
- 10 (b) wherein any two of R^b, R^c, and R^d are adjacent, together with their ring carbons form a C₆ or C₁₀ aromatic fused ring system;
- 15 (c) wherein any two of R^b, R^c, and R^d are adjacent, together with their ring carbons form a C₅-C₇ fused cycloalkyl ring having up to two double bonds including the fused double bond of the Ar group, which cycloalkyl ring can be substituted by one or more of the group consisting of alkyl, alkoxycarbonyl, amino, aminocarbonyl, carboxy, fluoro, or oxo;
- 20 (d) wherein any two of R^b, R^c, and R^d are adjacent, together with their ring carbons form a fused five to eight membered heterocycle, , wherein the ring fusion is at a carbon-carbon double bond of Ar, wherein the fused heterocycle consists of ring atoms selected from the group consisting of carbon, nitrogen, oxygen, and S(O)_n wherein n=0,1, or 2; and
- 25 (e) wherein any two of R^b, R^c, and R^d are adjacent, together with their ring carbons form a fused five or six membered heteroaryl ring, wherein the ring fusion is at a carbon-carbon double bond of Ar, wherein the fused heteroaryl ring consists of ring atoms selected from the group consisting of carbon, nitrogen, oxygen, and sulfur; and
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10. The method of claim 9, wherein Ar is not tetrazole, or pyrrole.

11. The method of claim 9, comprising administering an intraocular pressure decreasing or accommodation improving amount of a compound of formula II, wherein R^6 is according to $-\text{CH}(R^5)-\text{W}-\text{Rs}$

12. The method of claim 9, wherein aryl, Ar or Ar^* is substituted with, in addition to any substitutions specifically noted, one or more substituents selected from the group consisting of hydrogen, alkyl, amino, dialkylamino, 1-pyrrolidinyl, 4-[C_6 or C_{10}]arylpiperazin-1-yl, 4-[C_6 or C_{10}]arylpiperidin-1-yl, azetidin-1-yl, and morpholin-4-yl, piperidin-1-yl.

13. The method of claim 9, wherein $\text{Y}-\text{Ar}^\oplus \bullet \text{X}^-$ is



(III)

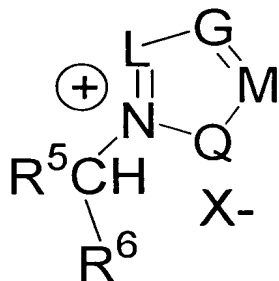
wherein G is O, S, or $\text{N}-\text{R}^a$;

M is N or $\text{C}-\text{R}^b$;

Q is N or $\text{C}-\text{R}^c$; and

L is N or $\text{C}-\text{R}^d$.

14. The method of claim 9, wherein $\text{Y}-\text{Ar}^\oplus \bullet \text{X}^-$ is



(IV)

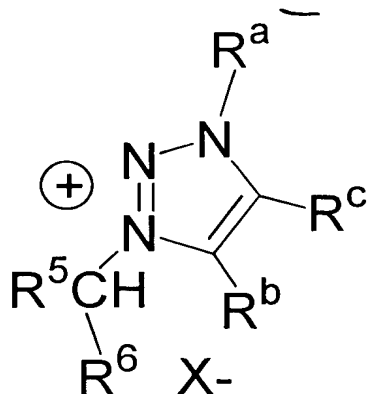
wherein G is N or $\text{C}-\text{R}^c$;

M is N or $\text{C}-\text{R}^b$;

Q is O, S, or $\text{N}-\text{R}^a$; and

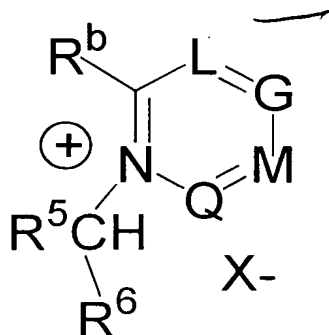
L is N or C-R^d.

15. The method of claim 9, wherein Y-Ar[⊕] • X⁻ is



(IV)

16. The method of claim 1, wherein Y-Ar[⊕] • X⁻ is



(V)

wherein L, G, M, Q, or R are independently N, C-R^c, C-R^d, C-R^e, C-R^f,

wherein

1. R⁵ is H;
2. R⁶ is
 - (1) cyano or
 - (2) a group of the formula -W-R⁷, wherein R⁷ is alkyl or Rs, and W is -C(=O)- or -S(=O)-;
3. R^b, R^c, R^d, and R^e are
 - (a) independently selected from the group consisting hydrogen, acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, (C₁-C₃)alkylenedioxy, alkylsulfonyl, alkylsulfinyl, ω-alkylenesulfonic acid, alkylthio, allyl, amino, Ar^{*}C(O)-, Ar^{*}O-, Ar^{*}-, Ar^{*}-alkyl-,

carboxy, carboxyalkyl, cycloalkyl, dialkylamino, halo, trifluoromethyl, hydroxy, (C₂-C₆)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid (SO₃H), 1-pyrrolidinyl-, 4-[C₆ or C₁₀]aryl piperazin-1-yl-, 4-[C₆ or C₁₀]aryl piperidin-1-yl, azetidin-1-yl, and morpholin-4-yl, piperidin-1-yl;

(b) where any two of R^b, R^c, R^d, and R^e are adjacent, together with their ring carbons form a C₆- or C₁₀- aromatic fused ring system;

(c) where any two of R^b, R^c, R^d, and R^e are adjacent, together with their ring carbons form a C₅-C₇ fused cycloalkyl ring having up to two double bonds including the fused double bond of the Ar group, which cycloalkyl ring can be substituted by one or more of the group consisting of alkyl, alkoxycarbonyl, amino, aminocarbonyl, carboxy, fluoro, or oxo;

(d) wherein any two of R^b, R^c, R^d, and R^e are adjacent, together with their ring carbons form a fused five to eight membered heterocycle, wherein the ring fusion is at a carbon-carbon double bond of Ar, wherein the fused heterocycle consists of ring atoms selected from the group consisting of carbon, nitrogen, oxygen, and S(O)_n wherein n=0,1, or 2;

(e) wherein any two of R^b, R^c, R^d, and R^e are adjacent, together with their ring carbons form a fused five or six membered heteroaryl ring, wherein the ring fusion is at a carbon-carbon double bond of Ar, wherein the fused heteroaryl ring consists of ring atoms selected from the group consisting of carbon, nitrogen, oxygen, and sulfur, and

wherein Ar has no more than three nitrogen atoms in the ring.

17. The method of claim 1, wherein Ar is substituted on a said ring nitrogen with amino.

18. The method of claim 17, wherein Ar is further substituted with up to two aminos.